Lautenbach (B. F.)

with author's compliments

ON A NEW FUNCTION

OF

THE LIVER.

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WHEN the portal vein of an animal is tied immediately before its entrance into the liver, the animal passes into a state resembling that following a fatal dose of one of the narcotics,—morphia, for example,—from which it differs, however, in that there is not a direct production of sleep, but an abolition of sensibility which predisposes to sleep. The animal remains in this state until its death, which occurs—always without convulsions—in the dog in from a half an hour to four hours, and in the rabbit and cat even earlier.

Usually after death the spleen is found enormously gorged with blood, as are also the walls of the stomach and intestines.

The liver, on the contrary, is found to contain almost no blood, being much paler than normal. The gall-bladder is empty.

At times the engorgement is but slightly developed, or entirely absent, in which cases I have always found a communication of one of the veins of the portal circulation with one of those of the general circulation, this easily explaining why the stasis did not occur. In one experiment where this engorgement was not found, the vena parumbilicalis (Schiff, Sappey)—which exists in mammals throughout life—was very much enlarged, and a communication of it with one of the mesenteric veins was also very large, thus forming a new portal circulation.

In a series of experiments, a large number of which were made in connection with Professor Schiff, I tied the vena porta of mammals nearly sixty times, and always obtained the same symptoms. These symptoms are in brief the following:

A great tendency to sleep, owing to the abolition of both tactile and general sensibility.

A diminished frequency in the beat of the heart, and an increased, followed by a decreased, arterial pressure.

Paresis of the heart-arresting fibres of the pneumogastrics, so that irritation of the sympathico-vagi trunks will no longer cause cessation of the heart's movements. In this connection it must be stated that,

following the ligature, contractions of the diaphragm occur isochronous with the beat of the heart, and disappear when the left phrenicus is lifted off the pericardium, to occur again when this is again brought in contact with the heart. I have frequently observed this symptom in animals that have been poisoned with drugs which produce paralysis of the heart-arrestors; and I have shown* that this phenomenon is due to an electrical current which is developed in the muscles of the heart and conducted by the left phrenic nerve (the right not being in contact with the pericardium, its presence or removal has no effect on the contractions) to the diaphragm.

A great diminution in the number of the respiratory movements, which frequently become stertorous.

Shortly before death a most curious symptom can frequently be observed. The animal has ceased to respire for several minutes, there is no heart-beat to be felt, and to all purposes the animal is dead: if, however, you now draw on the trunk of the carotid slightly downwards, the animal frequently commences again to breathe, and the heart-beat again becomes manifest, to cease again after several minutes. Should artificial respiration be resorted to, the beat of the heart would continue for an indefinite period of time.

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* Phila. Med. Times, March 31 1877, p. 296.

In the cold-blooded animals a different result is obtained. I have extirpated the livers of more than a hundred frogs and found none of the characteristic symptoms which occur after tying the vena porta in mammals; but, as will be shown later, evidence enough was obtained to show that the system was no longer in its normal state. This is also indicated by the circumstance that in a number of experiments where the hepatic vena cava (vena porta) of frogs was tied, similar results to those following the same operation in mammals were obtained.

Having seen the effects that ligature of the vena porta produces, it remains now to seek their cause.

That they are not due to the accumulation of blood in the portal circulation and a consequent diminution in the quantity going to the other portions of the body was determined in the experiments where I tied the hepatic veins, which carry all the blood from the liver to the vena cava, and found that this produced absolutely no symptoms.

If death in these cases were due to anæmia, convulsions would invariably precede the fatal termination; yet I have never met with convulsions following this operation. The study of the arterial pressure also shows that this theory is not the true one. On watching the blood-pressure in the manometer it is found that

after the ligature the column of mercury rises to nearly double the height it had before.

Nor do the symptoms occur when the biliary ducts are ligated; and consequently they cannot be explained on a theory of a retention of the biliary matters in the system.

Again, the symptoms cannot be due to the formation, through decomposition, of sepsin in the liver, as, (1) the formation of this poison occupies a much longer time than the time which expires after the application of the ligature up to the appearance of the symptoms; (2) the expressed juice, so to speak, of the liver of an animal that has been killed by tying its vena porta has absolutely no poisonous properties; (3) in the experiments where the vena porta was tied and by means of a tube blood was passed from the renal artery into the portion of the porta above the ligature, thus supplying the liver with blood enough to certainly prevent decomposition, the animals died even more rapidly than when this was not done.

It is hardly necessary to state that the ligature of the vena cava produces none of the characteristic symptoms which follow the vena porta ligature.

Having given and disproved some of the theories which may possibly be advanced to explain the interesting symptoms following this ligature, there remains

to be given that which I believe to be their true explanation.

Certain animals—some of the snake species and many insects—secrete normally, and others—the dog and cat in the hydrophobic state—secrete under pathological conditions very virulent poisons, the presence of which in some animals and not in others has never been satisfactorily explained. May its explanation not be found in the results of the experiment to which I have just alluded? *i.e.*, may not all animals have a poison formed in their system, which were it not excreted, as in the snakes and other animals, or destroyed by certain organs, the animals would rapidly succumb under its influence?

In this paper an attempt will be made more especially to prove that the symptoms following ligation of the vena porta are due to the accumulation in the blood of a poison which under normal conditions is destroyed by the liver.

If such a poison exists in the blood of an animal in whom the vena porta has been tied, the injection of a small quantity of this blood, though of course it could have no effect on any of the higher animals,—the operated animal dying just as soon as a sufficient accumulation of the poison has taken place to produce a cessation of the vital processes, and no fractional portion of its blood could possibly have decided effect on another animal of its class,—

might have some effect on the frog, and especially on the frog whose liver had been extirpated.

In thirty-four experiments I injected from one and a half to three cubic centimetres of blood taken from the vena porta, the vena cava, the vena jugularis, and from the right ventricles of dogs dying from ligature of the vena porta, into the lymph-sacs of the thighs of frogs, and these animals always exhibited symptoms analogous to those following the ligature of the vena porta in the higher animals, and almost always died within three hours.

As control-experiments, venous blood was always taken from the animal whose vena porta was about to be ligated, and injected into liverless frogs, and never were there any symptoms to be observed.

Nor did the blood of animals in whom the vena cava was tied, or from animals in whom a sling was placed around the vena porta without its being ligated, produce the slightest effect on frogs.

The following are illustrative experiments:

Animal.	Injection.	Operation.	Time.	Symptoms.
Dog, 22 lbs.		A sling around the vena porta; not ligated.	3, 3, 1877. 4.20	

Animal.	Injection.	Operation.	Time.	Symptoms.
R. esculenta. R. temporaria.	2 c.c. of blood from the v. jugularis was injected into two frogs in whom the liver had been extirpated.		3, 4, 1877, 10.04	
			11.00	No symptoms.
			12.00	No symptoms.
			3.00	No symptoms have been produced in either the dog or the frogs.
		Vena porta ligated.	3.35	
			3.45	Animal has passed into a state of somnolence. Irritation of the pneumogastrics does not produce arrest of the heart-beat.
R. esculenta. R. temporaria.	2 c.c. of blood from the vena jugularis was now injected into two other frogs in whom the liver had been removed.		3.48	
			3.54	When placed on their backs the frogs are unable to re-attain the abdominal position. All the movements are incoordinate.
			4.22	The animals are dead.

The blood of an animal in whom the vena porta has been tied must therefore contain a violent poison which does not exist to an appreciable extent in the blood of normal animals, but accumulates just as soon as the vena porta is tied.

All attempts which I have made to isolate this poison have proved futile, owing to its great volatility or destructibility; heating the blood but slightly in a water-bath is frequently sufficient to cause it to lose its poisonous properties.

It will no doubt occur to the reader, as it did to the author, that the vena porta poison is not the only poison which can be destroyed in its passage through the liver. Having frequently observed in my experiments with nicotine that it is almost impossible to kill an animal by giving this drug by the mouth, it seemed plausible that this is such a poison.

NICOTINE.—Having determined that one drop of this poison injected into the general circulation would kill even a large-sized dog, the author in a number of dogs injected this poison so that it had to pass through the liver before it could enter the general circulation. This was done sometimes by injecting into the small intestine, and sometimes by injecting into the mesenteric and splenic veins.

The following are the results obtained by this method of experimentation:

One drop of nicotine injected into the

mesenteric or splenic vein of a dog produces deep sonorous respiratory movements; an increased frequency and feebleness in the heart-pulse, so that at times it becomes imperceptible; retraction of the bulb of the eye, and a protrusion of the nictitating membrane; but the most characteristic symptom is the loss of sensation and especially the loss of the sense of touch. The animal in this respect resembles an animal in whom both the anterior hemispherical lobes of the brain have been extirpated; in walking it evidently does not feel the floor, as it frequently rests on the dorsal instead of on the plantar surface of its feet, and strong electrical irritation of the sciatic nerve does not dilate the pupil, this latter being the most delicate test to determine the absence of sensibility. Usually in fifteen minutes, but certainly in an hour, the animal has recovered, and acts like a normal dog. Even two drops of nicotine fail to kill a dog when injected into one of the veins of the portal circulation, or, what is really the same thing, into the intestine.

An injection of one drop of this drug into the subcutaneous connective tissue, or into a vein of the general circulation, produces all the symptoms just given as being present when the injection is made into one of the veins of the portal circulation; but, in addition, intense prostration, trismus, general tetanus, and death frequently

occur within one minute after the injection.

These results will be best seen in the following experiment:

Animal.	Injection.	Symptoms.
Dog, 10 lbs.		Respirations, 18–21. Pulse, 120. Temperature, 39°.60 (C.)
Time.		
11.55	Nicotine one drop into a mesenteric vein.	In a very short time the pulse rose to 204; the respirations became sonorous, the temperature descended to 37°.97 (C.) Retraction of the bulb of the eye and protrusion of the third membrane. On walking, the dog shows symptoms of a loss of the tactile sense; *i.e.*, the animal drags its feet, and frequently sets them down on their dorsal instead of on their plantar surface.
12.10		Respirations very strong; pulse 156, feeble, and felt only during inspirations.
12.35		Pulse 150; respirations 22; pupil small and reacts to light.
12.40		Pulse 23, resp. 20.
1.00		The dog has completely recovered.
1.50	Nicotine one drop into a mesenteric vein.	Immediately after the injection,—pulse 37, 36, 25, 22, 19, 15, in ten seconds; loss of tactile sense; respirations sonorous. Nictitating membrane protruded.
2.40		The dog has again recovered.

Animal.	Injection.	Symptoms.
5.07	Nicotine one drop into a subcutaneous vein of the posterior extremity.	Tetanus; trismus; pulse 210; respiration difficult. Death in one minute.

In the normal dog one-half drop of nicotine never produces death; but in dogs whose vena porta has been tied the author found that trismus and tetanus were produced, and death usually rapidly occurred, when but one-fifth drop was injected.

In normal frogs of the esculenta and temporaria species, an injection of one-tenth drop of nicotine into the general circulation always caused death under similar symptoms to those occurring in mammals. One-twentieth drop always produced marked symptoms, but never death. In frogs, however, whose livers had been extirpated, even one-fortieth drop produced death, as will be seen in the following experiment:

Animal.	Injection.	Operation.	Symptoms.
R. esculenta. Feb. 1, 1877.	Nicotine one-twentieth drop into the lymph-sac of the thigh.		

Animal.	Injection.	Operation.	Symptoms.
Feb. 2, 9.14 A.M.		Extirpation of the whole liver.	The animal was slightly ill, but soon recovered.
10.00	Nicotine one-thirtieth drop into the lymph-sac of the thigh.		
10.04			All voluntary movements have ceased. Pulse reduced from 48 to 27. Paralysis of the tactile sense.
10.16			The frog is dead. Nerves and muscles respond to irritation.

How else can these experiments be explained except on the theory that the presence of the liver is necessary for the destruction of the poison? The word destruction, and not elimination, is employed, because the author found that tying the gall-ducts of the frog did not in the least influence the quantity of the poison necessary to produce death.

In a large number of experiments one-fortieth drop of nicotine was injected into normal frogs without producing any symptoms whatsoever. Four hours after the injection the entire livers of the animals were removed, and twenty-four hours later one-fortieth drop was again injected, when, under symptoms of nicotine-poisoning, the animals died.

Against these latter experiments it cannot be said that possibly a second dose is more poisonous than the first, as I always found in unoperated animals the symptoms following a second much less marked than those following the first injection.

One-fifth drop of the drug injected into the intestine of a frog produced slight symptoms of loss of sensibility, but if now the liver of the frog was removed, and a day later the same dose again injected into the intestine, rapidly fatal symptoms were produced.

In the next series of experiments my object was to see if the fatal dose remained the same when the activity of the liver was increased by being placed in a hyperæmic state. To make the liver hyperæmic the author availed himself of an anatomical peculiarity in the frog. In the frog the liver does not receive the whole venous blood of the abdomen: only a portion of it is carried to the organ by the hepatic vena cava, while another portion is conveyed directly to the heart by a second vena cava without passing through the liver. To produce hyperæmia of the liver it is sufficient to force all the venous blood of the abdomen to traverse the liver; and that was accomplished by tying the second or superior vena cava.

When now one-tenth drop—the fatal dose for a frog—was injected, not the slightest symptom was observed, nor would

one-fifth drop produce death. From this we see that a greater activity of the liver causes a larger quantity of the poison to be destroyed.

The following experiment is characteristic of this series of experiments:

Animal.	Injection.	Operation.	Symptoms.
R. esculenta.		Ligature of second v. cava.	
Time.			
9.17			
11.00	Nicotine one-tenth drop into the lymph-sac of the back.		
1.25			No symptoms have occurred up to this time.
2.00			No symptoms
3.00			No symptoms

The following experiment shows that in the normal frog one-tenth drop of nicotine produces death:

Animal.	Injection.	Symptoms.
R. esculenta.	Nicotine one-tenth drop into lymph-sac of the back.	
Time.		
9.03		Slowing of the pulse, abolition of the tactile sense, and absence of voluntary movements.
9.31		Death.

Thinking it possible that the mere intimate contact with the liver-substance would be sufficient to cause the nicotine to lose its poisonous properties, the author made a large number of experiments by macerating the livers of dogs and rabbits with from three to five drops of nicotine, the expressed juice of the macerated mass then being injected into dogs and frogs. As will be seen in the following experiments, the fatal symptoms were, under these circumstances, never produced:

(1). "The liver of a newly-killed rabbit was taken and macerated with ten cubic centimetres of water and three drops of nicotine. The expressed juice of this mass was then injected into the cellular tissue of the posterior extremity of a dog weighing eleven pounds.

"In a short time the dog showed the respiratory symptoms; the protrusion of the third conjunctival membrane; dilatation of the pupil and the loss of the tactile sense; but none of the alarming narcotic and tetanic symptoms occurred; and in several hours the dog had recovered."

(2). "The liver of a dog who had died forty-eight minutes after his vena porta had been tied, was macerated with three drops of nicotine, and one-third of the expressed juice was injected into each of three liverless frogs.

"After thirty minutes, slight symptoms of nicotine-poisoning appeared, but these symptoms soon passed off."

After having found that the expressed juice of the kidney itself is not poisonous, the author as control-experiments macerated the kidneys of healthy animals with but two drops of nicotine, and the expressed juice produced the death of the animals into whom it was injected.

From these facts the author feels justified in believing that nicotine contains two poisons, one of which produces the non-fatal symptoms which so closely resemble those of locomotor ataxia. This poison is not at all affected by the liver. The other poison producing the tetanic symptoms and rapid death is entirely destroyed in passing through the liver.

Another explanation which we may get from these experiments is of the comparative absence of danger which attends the bringing of tobacco into the stomach through tobacco-chewing, as compared to the danger of inhaling the fumes of tobacco into the lungs. In the latter case the nicotine directly enters the general circulation, while in the former, owing to its having to pass through the liver, but little of the poison can enter the circulation.

Hyoscyamia.—In examining the other poisons for one which was wholly destroyed in passing through the liver, hyoscyamia was found to be such a one. One-half to three-quarters of a grain of this alkaloid will always kill a dog when introduced into the general circulation, under symp-

toms of diminution in the frequency of the pulse; paralysis of the sense of touch; paralysis of the heart-arresting fibres of the pneumogastrics; great somnolence, and even coma. In the experiments where one grain was injected into the portal circulation of dogs, absolutely no symptoms were produced; *i.e.*, a more than fatal dose had no effect when forced to pass through the liver before entering the general circulation.

The expressed juice from the livers of dogs, macerated with two to five grains of hyoscyamia, was injected into the general circulation of dogs and frogs, and no symptoms occurred. When, however, the kidney or spleen of a dog is macerated with but one grain of hyoscyamia, and the expressed juice is injected into dogs and frogs, these animals die under symptoms of hyoscyamia-poisoning.

In the frog one-twenty-fifth drop produces death under symptoms similar to those produced by the drug in the higher animals, with the addition of a very marked and peculiar slowing of all the movements of the animal. Following irritation of the nerves a longer time elapses before the muscles commence to contract, and when contracted they remain so longer than the contraction following the irritation of the nerves of an animal not poisoned.

One-fortieth drop produces but slight

symptoms in the frog. If however, the same frog was taken twenty-four hours later and the liver extirpated and then but one-sixtieth drop of the drug injected, the animal showed very marked symptoms and died, thus showing again that the absence of the liver causes a much smaller dose of the drug to be poisonous than when this organ is present.

Hyoscyamia produces one symptom in the liverless frog which it does not produce in the normal frog. If we examine a frog who has been poisoned by hyoscyamia after the liver had been removed, we find that reflex movements continue until near death; but if we attempt to irritate the sciatic nerve we find the strongest electrical currents will not produce contraction of the muscles. That is, a nerve which is still able to conduct the impulse necessary to produce a reflex movement is itself not excitable by direct irritation. The explanation of this result will be found in the difference between the receiving and conducting powers of the nerves to which I have recently drawn attention.*

Some of the experiments which I made gave such strange results that it seemed as if some source of fallacy must exist. Carefully repeating these experiments again and again, and always obtaining the same results, convinced me that all doubts were

* Philadelphia Medical Times, vol. vii. No. 243.

unfounded. These experiments are so interesting that one will be given in full.

"At twenty minutes before two, one-sixtieth drop of hyoscyamia was injected into the lymph-sac of the thigh of a medium-sized frog of the esculenta variety. Slight slowing of the movements was the only symptom. At 4.00, the animal was as before the injection. At 4.55 its liver was extirpated, and at 4.58—but three minutes later—the animal showed great slowness in all its movements. When the posterior extremities were extended, in response to a slight irritation, it took 8" for them to return to their normal position. When the animal was placed on its back it could not re-attain its abdominal position. In one hour the animal was perfectly motionless, and in three hours its heart had ceased to beat. After death, irritation of the nerves no longer produced contractions of the muscles; but direct irritation of the latter caused their contraction."

In this experiment the injection of the poison produced very slight symptoms, which disappeared after several hours. One hour after their disappearance the liver of the frog was removed, when immediately, and without any more of the poison being given, the animal showed intense symptoms of hyoscyamia-poisoning, followed by death.

For some time I was at a loss for a plausible theory to explain the results obtained in

the experiments similar to the one just given. The hyoscyamia was circulating in the blood, and reaching all the organs which it could affect, in no greater quantity after than before the extirpation of the liver, and consequently it alone could not have produced these marked symptoms. There must have been another poison formed in the frog, which, combined with the small quantity of hyoscyamia still in the blood, produced these fatal symptoms. This poison could have been none other than the poison which I spoke of in mammals as the vena porta poison, thus showing that, though extirpation of the liver in frogs does not produce manifest symptoms, yet a poison is thereafter retained in the system which would have been removed by the liver had not this organ been extirpated.

We have seen from the previous experiments that neither of these two poisons alone—*i.e.*, neither the extirpation of the liver nor the injection of one-sixtieth drop of hyoscyamia—could produce this result in frogs, but a combination of the two, before the system had time to become accustomed to the presence of the "vena porta" poison, was necessary to produce the fatal result.

The great similarity in the effects of these two poisons is remarkable.

Hyoscyamia slows the movements, as also does the vena porta poison.

They both modify sensation.

They both produce a tendency to sleep.

They both paralyze the heart-arresting fibres of the pneumogastrics.

With either alone the nerves remain excitable until long after death, but with a combination of the two the nerves are still able to conduct impressions from the centres to the periphery, and thereby produce movements, but it is impossible to cause the nerves to conduct impressions applied to their trunks.

In the author's further experiments with hyoscyamia it was found that, while one-twenty-fifth of a drop was fatal to normal frogs, one-fifteenth did not produce dangerous symptoms in frogs whose livers had been rendered hyperæmic by tying the second vena cava.

In hyoscyamia we have, therefore, an organic poison which is destroyed by the liver, as the author's experiments will certainly allow of no other conclusion.

Conia is another drug whose active properties the author found to be destroyed by the liver. As the experiments are not essentially different from those made with hyoscyamia, it will not be necessary to infringe on the reader's time and patience by giving them.

Recently, through the kindness of Dr. Mitchell, the author obtained a small quantity of the *venom of the cobra-snake*, with which a new series of experiments were made.

A fatal dose of this poison injected into

the mesenteric vein of a cat produces no symptoms, although the same dose kills the same cat if introduced into the general circulation some hours after.

A dose which had produced no effect on a frog killed this frog when its liver had been removed.

A fatal dose was no longer fatal when the liver of the frog was made hyperæmic by tying the second vena cava.

The venom of the cobra snake is, therefore, also a poison whose active properties are destroyed by the liver. This is extremely interesting, as it will explain why the animal poisons when swallowed produce no symptoms.

Among the drugs which the author has found not to have their effect modified by the liver are curare, prussic acid, and atropia. As regards the latter, some doubts may be expressed, as it and hyoscyamia are frequently considered to be one and the same alkaloid; but this is not so, as the two differ in a number of respects as regards their physiological action.

The experiments which have been given show distinctly that some of the organic poisons are destroyed in passing through the liver, and it is probable that the number of poisons thus destroyed will not prove to be inconsiderable, it being a well-known fact that many of the alkaloids do not have the same effect when given by the mouth as when given hypodermically. By

the former method the greater portion of the drug has to pass through the liver on its way to the general circulation, while by the latter all enters directly into the general circulation. It must not, however, be thought that every drug which does not produce its effects when given by the stomach is destroyed by the liver; as it is possible that they are not absorbed from the alimentary canal. This the author has found to be the cause of the non-action of curare and of the but partial action of atropine when thus given.

Before closing this article there is still one symptom to speak of that frequently follows the extirpation of the liver in frogs, which shows that, though this operation produces no symptoms which are apparent at first, nevertheless a poison is developed and operative.

Goltz,* nine years ago, found that when he removed the cerebrum of frogs and rubbed a smooth object along the back of the animal, or when he merely laid the animal on its back, it croaks each time that its back is rubbed, so that it would not be difficult to have the frogs of Aristophanes: any physiologist could with very little trouble have a frog chorus that would, to the amusement of the public, let their voices be heard when wished for. I have found that extirpation of the cerebrum

* Functionen d. Nervencentren des Frosches, p. 1.

is not necessary for the production of this symptom, but that the section of one of the pedunculi cerebri is all-sufficient. In the unoperated frog this croaking cannot be produced.

Goltz explains this experiment by saying that the rubbing excites reflexly the centres of the voice existing in the medulla oblongata, and when this is no longer influenced by the cerebrum, croaking will result; but when the cerebrum is present, this acts as an arrestor of reflex action, and consequently the croaking does not occur.

Many frogs who have been liverless for some days, when placed or when rubbed on their back croak even more constantly than a frog whose cerebrum has been removed. Of course no one would from this experiment be likely to infer that the liver is an arrestor of reflex action, although its removal causes an arrest on the reflex activity of the voice to be removed. But how then is the result obtained to be explained? The same symptom is to be observed in frogs poisoned with hyoscyamia. In these animals it must be due to some modifying influence which the drug has on the sensory-motor tracts of the brain, of which the fibres pass through the pedunculus on their way to the great gangliæ.

The same explanation must be given for the symptom occurring in liverless frogs, *i.e.*, a poison is also accumulated in these

animals which, after several days, paralyzes the arresting influence which the cerebrum has on the reflex activity of the voice.

The experiments alluded to in the preceding paper have brought the author to the following conclusions:

1. *The liver has for one of its functions the office of destroying certain of the organic poisons.*

2. *A poison is being constantly formed in the system of every animal which it is the office of the liver to destroy.*

The experiments—two hundred and eighty-three in number—forming the basis of the foregoing paper were almost all made in the Physiological Laboratory of Professor Schiff, at Geneva, for whose kind assistance and advice the author most gratefully acknowledges his obligations.


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